Cardiac Contractility

By

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By the end of this lecture the student will be able to:

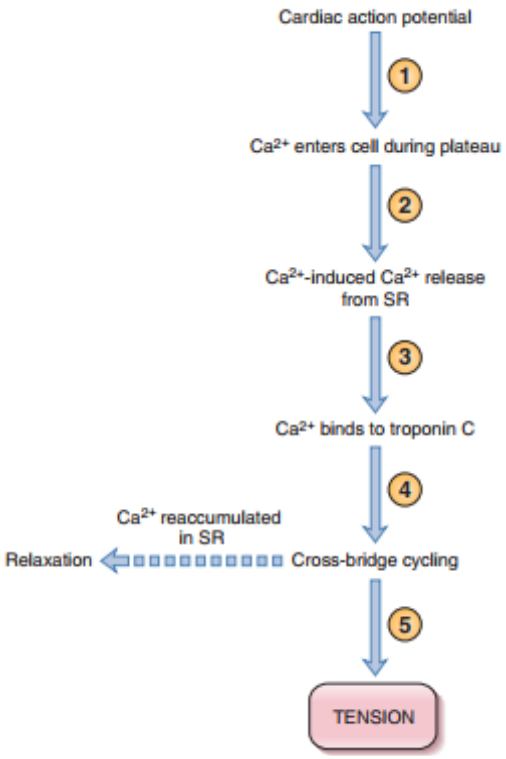
1. Explain the functional similarities and differences between skeletal and cardiac muscle.
2. Describe the excitation-contraction coupling of the cardiac muscle.
3. Explain the different factors affecting contractility (preload, afterload, heart rate, nervous; sympathetic and parasympathetic and chemicals; neurotransmitters, hormones, ions and drugs).
4. Apply the information studied in this section to solve a clinical problem or explain a cardiac muscle contractile response.

Functional similarities and differences between the cardiac and skeletal muscles:

- Both are striated.
- Both are composed of **sarcomeres.**
- In both the sarcomeres, which run from Z line to Z line, are composed of **thick and thin filaments**.
- The **thick filaments** are composed of **myosin,** whose globular heads have actin-binding sites and ATPase activity.
- The **thin filaments** are composed of three proteins: actin, tropomyosin, and troponin. **Actin** with a myosin-binding site. **Tropomyosin** runs along the groove of the twisted actin strands and functions to block the myosin-binding site. **Troponin** is composed of a complex of three subunits; the troponin C subunit binds Ca^{2+}. When Ca^{2+} is bound to troponin C, a conformational change occurs, which removes the tropomyosin inhibition of actin-myosin interaction.
- Contraction occurs according to the **sliding filament model,** which states that when cross-bridges form between myosin and actin and then break, the thick and thin filaments move past each other. As a result of this cross-bridge cycling, the muscle fiber produces tension.
- The cardiac muscle fibers are **short, branched**
- The **intercalated discs**, intercellular connections consists of tight and gap junctions is present in cardiac not skeletal muscle, responsible for the cardiac **functional syncytium** (to act as a unite, atrial syncytium and ventricular syncytium=both atria and both ventricles **obey to all or none law**).
- The **mitochondria**, which is the site of storage and release of ATP, are **more numerus and elongated** in cardiac than skeletal muscle.
- The **transverse** (**T**) **tubules** invaginate cardiac muscle cells **at the Z lines**, are continuous with the cell membranes, and function to carry action potentials to the cell interior, are **more developed** in cardiac than in skeletal muscle.
- The **sarcoplasmic reticulum,** which is the site of storage and release of Ca^{2+} for excitation-contraction coupling, are **less developed** in cardiac muscle than skeletal muscle.

Excitation-Contraction Coupling:

Definition: The process by which an action potential results in muscle contraction (production of tension). The following steps are involved in excitation-contraction coupling in cardiac muscle.



Excitation-contraction coupling in myocardial cells.

1. The cardiac **action potential** is initiated in the myocardial cell membrane, and the depolarization spreads to the interior of the cell via the T tubules.

- *Recall that a unique feature of the cardiac action potential is its **plateau**, which results from an **inward Ca^{2+} current** through L-type Ca^{2+} channels (**dihydropyridine=DHP receptors**) from extracellular fluid (ECF) to intracellular fluid (ICF).*

2. Entry of Ca^{2+} into the myocardial cell triggers the release of more Ca^{2+} from stores in the sarcoplasmic reticulum through *Ca^{2+} release channels (**ryanodine receptors**)*. This process is called **Ca^{2+}- induced Ca^{2+} release**.

- *The Ca^{2+} that enters during the plateau of the action potential is called the **trigger Ca^{2+}**.*
- *Two factors determine how much Ca^{2+} is released from the sarcoplasmic reticulum in this step:*
    1. *The amount of Ca^{2+} previously stored.*
    2. *The size of the inward Ca^{2+} current (trigger Ca^{2+}) during the plateau of the action potential.*

3. Ca^{2+} release from the sarcoplasmic reticulum causes the intracellular Ca^{2+} concentration to increase so, binds to **troponin C.**

4. Tropomyosin is moved out of the way, and the interaction of actin and myosin can occur then break (**cross-bridges cycling= binding, bending, detachment**), and tension is produced.

- *Cross-bridge cycling continues as long as intracellular Ca^{2+} concentration is high enough to occupy the Ca^{2+}-binding sites on troponin C.*
- *The magnitude of the tension developed by myocardial cells is proportional to the intracellular Ca^{2+} concentration.*

So, duration and amplitude of contraction depend on the availability of calcium.

- *Therefore, it is reasonable that **hormones**, **neurotransmitters**, and **drugs** that alter the inward Ca^{2+} current during the action potential plateau or that alter sarcoplasmic reticulum Ca^{2+} stores would be expected to change the amount of tension produced by myocardial cells.*

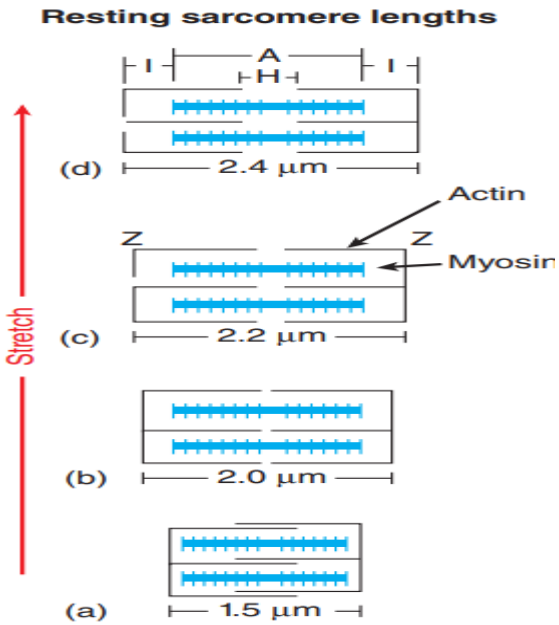
5. Relaxation occurs when Ca^{2+} is re-uptaken in the sarcoplasmic reticulum by the action of the Ca^{2+} ATPase pump, decreases the intracellular Ca^{2+} concentration to resting levels. In addition, Ca^{2+}, which entered the cell during the plateau of the action potential, is extruded from the cell by Ca^{2+} ATPase pump and Ca^{2+}-Na^{+} exchanger in the sarcolemma (These sarcolemmal Ca^{2+} ATPase pump Ca^{2+} out of the cell against its electrochemical gradient using ATP directly (an example of primary active transport), and the Ca^{2+}- Na^{+} exchanger using energy from the inward Na^{+} gradient (an example of secondary active transport).

Factors affecting Contraction:

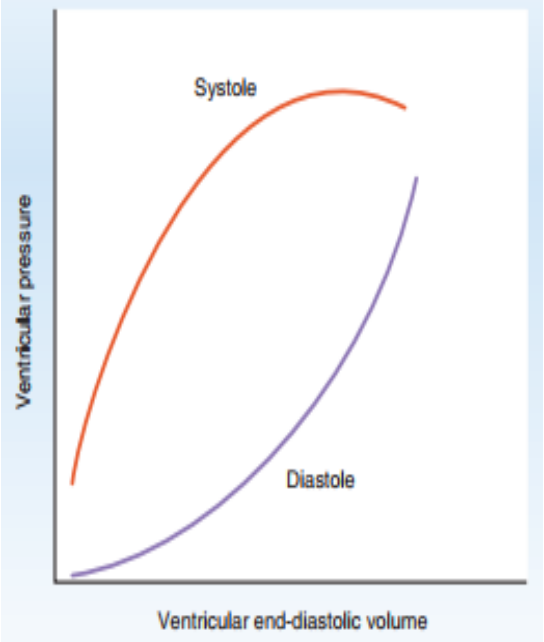
- **Positive inotropic agents**: agents that ***increase*** contractility by increasing intracellular Ca^{2+} availability.
- **Negative inotropic agents**: agents that ***decrease*** contractility by decreasing intracellular Ca^{2+} availability.

1- Effect of preload (Length-Tension Relationship):

- **Definition:** The maximal tension that can be developed by a myocardial cell depends on its resting length. The preload is the venous return.
- **Physiologic basis**: The degree of overlap of thick and thin filaments and the number of possible sites for cross-bridge formation (depends on the intracellular Ca^{2+} concentration). In myocardial cells, maximal tension development occurs at cell lengths of about 2.2 µm, or L-max. At this length, there is maximal overlap of thick and thin filaments.
- **The upper curve** is the relationship between ventricular pressure developed during systole and end diastolic volume (or end-diastolic fiber length). This pressure development is an active mechanism. On the ascending limb of the curve, pressure increases steeply as fiber length increases, reflecting greater degrees of overlap of thick and thin filaments, greater cross-bridge formation and cycling, and greater tension developed.
- The curve eventually levels off when overlap is maximal. If end-diastolic volume were to increase further and the fibers were stretched to even longer lengths, overlap would decrease, and the pressure would decrease (descending limb of the curve).
- This systolic pressure volume (i.e., length-tension) relationship for the ventricle is the basis for the **Frank-Starling relationship** in the heart.
- **The lower curve** is the relationship between ventricular pressure and ventricular volume during diastole, when the heart is not contracting. As end-diastolic volume increases, ventricular pressure increases through passive mechanisms. The increasing pressure in the ventricle reflects the increasing tension of the muscle fibers as they are stretched to longer lengths.



Frank Starling Law
(sarcomere length)

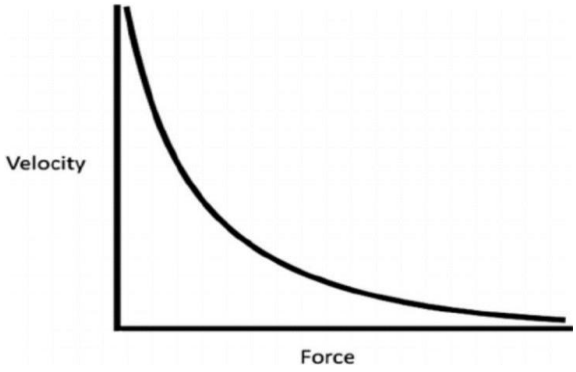


Systolic and diastolic left ventricular pressure volume curves.
The systolic curve shows active pressure.
The diastolic curve shows passive pressure.

2- Effect of afterload (Force-Velocity relationship)

◆ The **afterload** for the left ventricle is aortic pressure (for the right ventricle is pulmonary pressure). The ***velocity*** of shortening of cardiac muscle is maximal when afterload is zero, and velocity of shortening decreases as afterload increases. As cardiac muscle contracts against an afterload, its contraction occurs in 2 stages:

- Isometric contraction
- Isotonic contraction



Force-velocity relationship

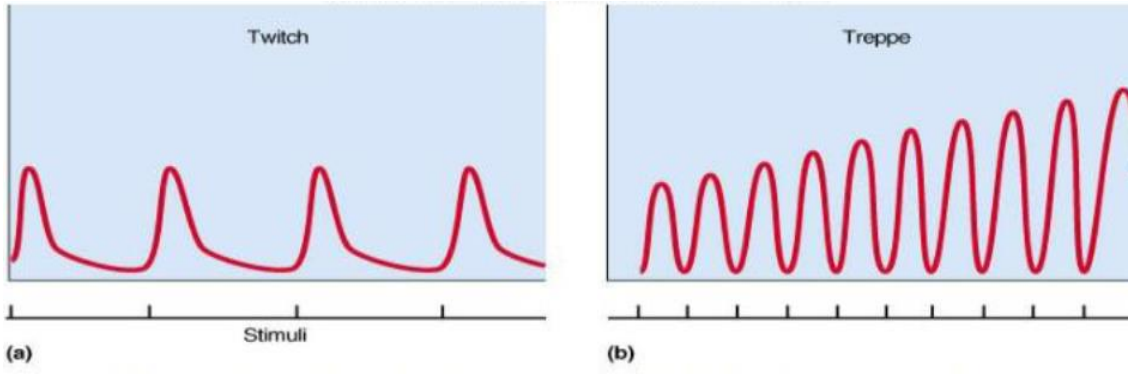
3- Effect of Heart Rate

Changes in heart rate produce changes in contractility (i.e. when the heart rate increases, contractility increases; when the heart rate decreases, contractility decreases).

➢ **Mechanism:** as contractility correlates directly with intracellular Ca^{2+} concentration during excitation-contraction coupling, **when heart rate increases:**
(1) there are **more action potentials per unit time** and an **increase in the total amount of trigger Ca^{2+}** that enters the cell during the plateau phases of the action potentials.

(2) there is **greater influx of Ca^{2+}** into the cell during the action potentials, the **sarcoplasmic reticulum accumulates more Ca^{2+} for subsequent release** (i.e., increased stored Ca^{2+}).

➢ **example** of the effect of heart rate on contractility, the positive staircase effect.



Example of the effect of heart rate on contractility. Tension is used as a measure of contractility. The frequency of the bars shows the heart rate, and the height of the bars shows the tension produced on each beat.

◆ **Positive staircase effect (Treppe):** When heart rate doubles, for example, the tension developed on each beat increases in a stepwise fashion to a maximal value. This increase in tension occurs because there are more action potentials per unit time, more total Ca^{2+} entering the cell during the plateau phases, and more Ca^{2+} for accumulation by the sarcoplasmic reticulum (i.e., more stored Ca^{2+}). Tension rises stepwise, like a staircase: With each beat, more Ca^{2+} is accumulated by the sarcoplasmic reticulum, until a maximum storage level is achieved.

4- *Effects of the Autonomic Nervous System*

◆ Sympathetic nervous system:

Stimulation of the sympathetic nervous system and circulating catecholamines have a **positive inotropic effect** on the myocardium (i.e., increased contractility), via activation of **β1 receptors,** which are coupled via a Gs protein to adenylyl cyclase. Activation of adenylyl cyclase leads to the production of cyclic adenosine monophosphate (cAMP), activation of protein kinases, and phosphorylation of proteins that produce the physiologic effect of increased contractility.

(1) There is phosphorylation of the sarcolemmal **Ca^{2+} channels (DHP)**. As a result, there is increased inward Ca^{2+} current during the plateau and increased trigger Ca^{2+}, which increases the amount of Ca^{2+} released from the sarcoplasmic reticulum.

(2) There is phosphorylation of a protein that regulates Ca^{2+} ATPase in the sarcoplasmic reticulum, resulting in greater uptake and storage of Ca^{2+} by the sarcoplasmic reticulum. Increased Ca^{2+} uptake by the sarcoplasmic reticulum has two effects: It causes faster relaxation (i.e., briefer contraction), and it increases the amount of stored Ca^{2+} for release on subsequent beats.

◆ Parasympathetic nervous system:

Stimulation of the parasympathetic nervous system and Acetylcholine have a **negative inotropic effect** on the ***atria,*** via **muscarinic receptors (M2),** which are coupled via a Gi protein to adenylyl cyclase, contractility is decreased by decreasing inward Ca^{2+} current during the plateau of the action potential and decrease the amount of Ca^{2+} released from the sarcoplasmic reticulum.

5- Effect of Hormones

Hormones have positive inotropic effect include **catecholamines, glucagon** (by increasing cAMP) and **thyroid hormone** (by increasing ATPase activity & increase sensitivity to catecholamines).

6-Effect of Ions

Sodium:

Hypernatremia (increased extracellular sodium) has **negative inotropic** effect. As hypernatremia favors Na^+ influx and Ca^{2+} efflux through the Na^+-Ca^{2+} exchanger, thus decreasing intracellular Ca^{2+} level, so decreasing force of contraction.

Hyponatremia (decreased extracellular sodium) has an opposite effect.

Calcium:

Hypercalcemia (increased extracellular calcium) has **positive inotropic** effect and may **stop the heart during systole** (Ca^{2+} rigor) (Spastic contraction). As the trigger Ca^{2+} influx increases, it increases sarcoplasmic Ca^{2+} release (CICR), so increasing the force of contraction.

Hypocalcemia (decreased extracellular calcium) has an opposite effect.

Potassium:

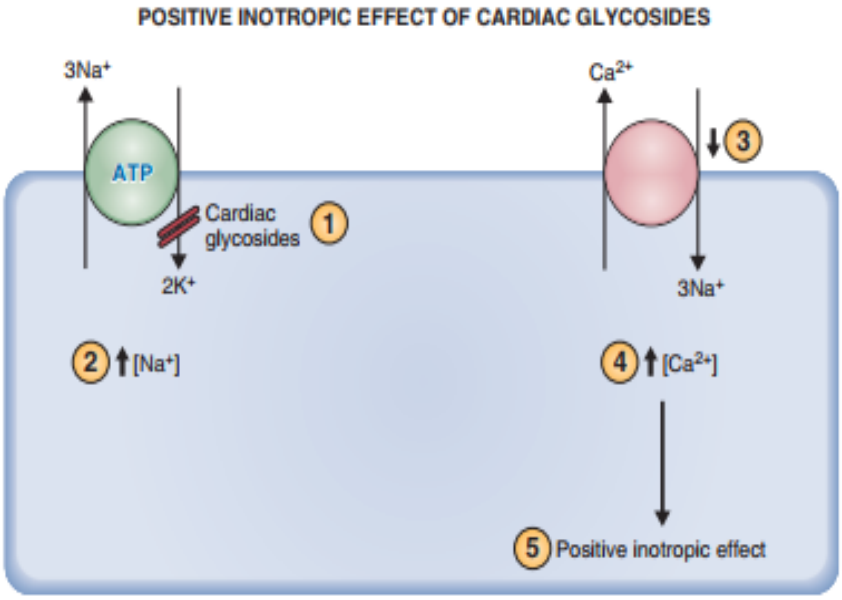
Hyperkalemia (increased extracellular potassium) has **negative inotropic** effect and may **stop the heart during diastole** (Flaccid or dilated heart). As the extra cellular K^+ concentration increases, the K^+ cannot out flux from the myocardial cell, so, the negativity of the membrane potential of the muscle fibers decreases, reducing the amplitude of action potential, decreasing Ca^{2+} influx, and in turn decreasing Ca^{2+} release from sarcoplasmic reticulum, so decreasing force of contraction.

Hypokalemia (decreased extracellular potassium) has an opposite effect.

7-Effect of Drugs

Cardiac glycosides are **positive inotropic** drugs. These drugs are derived from extracts of Digitalis (digoxin, digitoxin and ouabain). Cardiac glycosides **inhibit Na^+-K^+ ATPase** → less Na^+ is pumped out of the cell, increasing the intracellular Na^+ concentration → the inwardly directed Na^+ gradient decreases. As a result, Ca^{2+}-Na^+ exchange decreases because it depends on the Na^+

gradient. As less Ca^{2+} is pumped out of the cell by the Ca^{2+}-Na^{+} exchanger, the intracellular Ca^{2+} concentration increases → increase in tension (positive inotropic effect). The major therapeutic use of cardiac glycosides is in the treatment of ***congestive heart failure***.



Ca^{2+} channel blockers that hinder Ca^{2+} entry into the cell decreasing the force of contraction (negative inotropic drugs). Used in treatment of hypertension and arrythmia (irregular beats).

SUGGESTED TEXTBOOKS

Linda Costanzo from page 144-149